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Food allergy: A clinician's criteria for including sera in a serum bank

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Abstract

Safety assessment for genetically-engineered crop plants includes assessment for allergic responses. To facilitate this assessment, serum banks should contain well-characterised sera from patients with confirmed food allergies. A serum is defined as well-characterised if it is taken from a patient who has a convincing history of allergic responses to a known allergen or an allergen-containing food, a positive skin prick test (or elevated IgE response), and a positive response in a clinical food challenge.

Keywords: Allergen; Anaphylaxis; Genetically-modified; IgE; Oral allergy syndrome; Urticaria

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; LPT, lipid transfer protein; OAS, oral allergy syndrome; SPT, skin prick test

Article Outline

References

1. Introduction

New processing technologies for established foods and introduction of genetically-modified foods are changing the nature of our diet. Because of this, potentially allergic individuals are increasingly exposed to novel foods and proteins. The possible risk of allergenic responses to foods or proteins derived from genetically-modified crops is therefore a significant public health concern. Regulatory agencies recommend that genetically-modified foods undergo allergy assessment, including tests for IgE binding against sera from allergic subjects. This approach will identify food proteins that share significant amino acid sequence identity with known allergens (Taylor, 2006). Guidelines for assessment of allergenicity of GM crops have been published in three documents: the first comprehensive document was published by the international food biotechnology council (IFBC) in collaboration with the ILSI Allergy and Immunology Institute (Metcalfe et al., 1996); then, in 2001, the FAO/WHO published allergen testing recommendations (FAO/WHO, 2001) and in 2003, the Codex Alimentarius Commission guidelines were published (FAO/WHO, 2003). All three documents indicate that the primary risk is to individuals with existing allergies to known allergens. Thus, novel foods should avoid introduction of known allergens into the food supply.

Sera from patients with well-defined food allergies will be helpful for assessing the allergenicity of novel proteins. Which sera, however, should be included in serum banks for such testing? The aim of this article is to define from a clinician's point of view the criteria for using a serum to test allergenicity of novel proteins, and for including that serum in a serum bank.

2. Clinical manifestations of food allergy

Food allergy affects up to 8% of children and 2–5% of adults ([Osterballe et al., 2005] and [Zuberbier et al., 2004]). However, the prevalence of food allergy in the general population is overestimated, because food allergy is often associated with chronic and/or idiopathic symptoms and diseases, including chronic fatigue syndrome, irritable bowel syndrome, headache and psychological disorders. In contrast, clinical food allergy is a well-defined disease that involves clearly-defined clinical symptoms.

Serum banks should only include sera from patients with a consistent history of allergic reactions, while sera from patients with so-called “controversial symptoms” should be excluded (Ortolani et al., 1999).

The following text outlines the clinical symptoms of food allergy. Symptoms of food allergy generally appear within a few minutes up to 2 h following the ingestion of food. The allergic reaction may involve one or more target organs (i.e., skin, gastrointestinal tract, respiratory tract, cardiovascular system) (Sampson, 1999).

The skin is often involved in allergic reactions to food. Acute generalized urticaria, with or without angioedema are the most common clinical presentations of food allergy apart from the oral allergy syndrome (OAS). Skin reactions are frequently accompanied by reactions in other target organs, but may be present as the sole manifestation. Sometimes only a generalized flush (i.e., pruritic erythema) is observed. Furthermore, contact urticaria (a local wheal and flare reaction at the site of contact) is often observed. In contrast, chronic urticaria is rarely caused by food allergy.

Oral allergy syndrome is by far the most frequent clinical presentation of food allergy in adult patients (Mari et al., 2005). OAS involves contact urticaria confined to the lips and oropharyngeal mucosa. Symptoms generally appear within 1–15 min following food ingestion and include pruritus of the lips, tongue, palate, ears, and throat; mild angioedema at the same sites may be observed. Spontaneous resolution occurs within minutes in most cases, although some patients may subsequently develop a systemic reaction. OAS can be elicited by any food and is frequently observed in patients allergic to both pollen and fresh fruits, nuts or vegetables. This is because of IgE cross-reactivity to homologous proteins in pollen and fruits, nuts or vegetables. This clinical manifestation has been extensively reviewed recently (Mari et al., 2005).

Nausea, vomiting, abdominal cramps or diarrhea are manifestations of food allergy in the gastrointestinal tract. They are often accompanied by allergic manifestations in other target organs, but can also occur as isolated symptoms in children ([Bock and Atkins., 1990] and [Sampson, 2004]).

Similarly, allergic response in the respiratory tract including rhinoconjunctivitis, bronchospasm or laryngeal edema are rarely the sole manifestation of food allergy

(James et al., 1994). Acute asthma attacks associated with systemic anaphylaxis can be extremely severe, and are the most frequent cause of lethal food-induced anaphylaxis (Bock et al., 2001).

Anaphylaxis (Sampson et al., 2006), the most severe manifestation of food allergy, is a medical emergency. Anaphylaxis has been defined as a "*severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance"* or a "*serious allergic reaction that is rapid in onset and may cause death*." It is important to stick to those definitions since the term anaphylaxis is often misused.

A recent symposium was held to define simple straight-forward criteria for properly diagnosing >95% of anaphylaxis cases (Sampson et al., 2006). These criteria are summarised in Table 1 (Sampson et al., 2006.)

Table 1.

Clinical criteria for diagnosing anaphylaxis (according to Sampson, 2006)

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips–tongue–uvula) and at least one of the following: (a) Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) (b) Reduced BP or associated symptoms of end-organ-dysfunction (eg hypotonia (collapse), syncope, incontinence) 2. Two or more of the following symptoms that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours) (a) Involvement of the skin, mucosal tissue (eg generalized hives, itch-flush, swollen lips–tongue–uvula) (b) Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) (c) Reduced BP or associated symptoms of end-organ-dysfunction (eg hypotonia (collapse), syncope, incontinence)

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:
(d) Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting) 3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours) (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease in systolic BP

Full-size table

PEF: Peak expiratory flow, BP: blood pressure.

* Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

In food-dependent exercise-induced anaphylaxis, the intake of a specific food, or (more rarely) of any food, induces a generalized reaction only if the patient exercises within 2–4 h following ingestion. For example, several reports describe association between sensitisation to omega-5-gliadin and exercise-induced anaphylaxis to wheat ([Matsuo et al., 2004] and [Palosuo et al., 2003]).

3. Clinical diagnosis of food allergy

The first step in diagnosing food allergy is a detailed case history. This information is used to triage patients according to whether they are likely or unlikely allergic subjects. Information on concurrent respiratory allergies, in particular, to pollen, but also latex or house dust mites should be included in the case history.

Food-specific IgE antibodies can be assessed by *in vitro* assay or a skin prick test (SPT); these tests attempt to link the clinical symptoms with an IgE-mediated pathophysiology. Although these diagnostic tests can identify IgE antibodies for a specific food, they do not establish the diagnosis of food allergy. Ultimately, diagnosis

of food allergy requires a positive response in a controlled food challenge; this constitutes proof of the clinical relevance of the food-specific IgE.

4. Clinical tests for routine diagnosis of food allergy

The skin prick test (SPT) and *in vitro* assay for food-specific IgE are currently the primary tools for diagnosing food allergy (Sampson, 1999). While the SPT is inexpensive and rapid, its outcome is influenced by a variety of factors that are difficult to standardize. These include the source of the allergen, the use of commercially available food extracts versus the use of native foods for skin testing, the condition of the patient's skin, prick technique and patient's health and/or medications. Many commercial food extracts used for these tests lack appropriate biological standardization and are not adjusted for the content of specific allergens (Becker et al., 2006). This often leads to poor correspondence between test results, the clinical history and the results of a controlled food challenge.

In children with atopic dermatitis and class I allergy to foods containing stable allergenic proteins (*i.e.*, milk, egg, peanut, fish or wheat), SPT and *in vitro* IgE testing are sensitive methods, accurately detecting 90–100% of allergic patients (Sampson and Ho, 1997). Similarly, for these allergens, these tests also have excellent negative predictive value (*i.e.*, up to 95% accuracy for non-allergic patients; [Sampson and Ho, 1997] and [Niggemann et al., 2000]). Similar success is not achieved with other groups of patients or other foods. For example, for patients with pollen-related (class II) food allergy, the SPT and *in vitro* IgE testing is much less sensitive, especially when performed with a commercially available food extract. For tests performed with commercially available extracts from celery, carrot, cherry or hazelnut, the sensitivity of SPT and CAP-FEIA were 20–65% or 4–87%, respectively ([Ballmer-Weber et al., 2000], [Ballmer-Weber et al., 2001], [Ballmer-Weber et al., 2002] and [Ortolani et al., 2000]). Due to the high rate of false negative results and the low negative predictive value of these tests, they cannot be reliably excluding food allergy in that group of patients.

What are the implications of these findings for a serum bank? If the sole criterium for inclusion of a serum in a serum bank was the presence of IgE-reactivity to commercially available food extracts, many patients with true clinical food allergy

would be excluded. This in turn, might lead to false negative allergenicity testing for novel proteins in or derived from genetically-modified foods.

It should be emphasized that food allergy is a complex matter, and that the response to a food or an allergen test can differ from one group of patients to another (*i.e.*, children vs. adults or two geographically-defined subpopulations). For example, an *in vitro* IgE test for allergy to cherry had low sensitivity (20–25%) in patients from Switzerland or Germany ([Ballmer-Weber et al., 2002] and [Scheurer et al., 2001]) but achieved a sensitivity of 81% in patients from Mediterranean countries. The reason for this discrepancy is that patients from Mediterranean countries tend to react to lipid transfer protein (LTP) in cherry, which is a very stable allergen, whereas patients from Central Europe tend to react to Pru av 1, which is much less stable. Pru av 1 shares approximately 59% amino acid sequence identity with the major birch pollen allergen Bet v 1and is particularly susceptible to degradation during extraction (Vieths et al., 1998).

Moreover, even with well-prepared extracts, positive results can be obtained with the SPT and *in vitro* IgE testing, while negative results are obtained with DBPCFC. This can indicate either clinically-insignificant sensitization or cross-reactivity. Furthermore, these observations can explain the overall low specificity and low positive predictive value of SPT and *in vitro* IgE tests for food allergy ([Sampson and Ho, 1997] and [Niggemann et al., 2000]).

Since positive SPT or elevated level of food-specific IgE may indicate sensitization but not clinical allergy, sera should not be included in a serum bank solely on these criteria.

However, it is a major advantage that *in vitro* IgE tests can be used to quantify food-specific IgE (Celik-Bilgili et al., 2005). When the concentration of food-specific IgE is estimated repeatedly by this method, it is possible to monitor the progress of sensitisation or the development of tolerance to a specific antigen in an individual patient.

Furthermore, specific IgE levels have been identified as “decision points” for predicting the outcome of a food challenge or to predict clinical allergy (Niggemann et al., 2005). Such decision points have been defined for instance for egg and peanut

but not wheat and soy; however, inconsistent results were obtained in different clinical studies ([Celik-Bilgili et al., 2005], [Mehl et al., 2005] and [Osterballe and Bindslev-Jensen, 2003]). To date, decision points cannot reliably differentiate between tolerance and allergy in sensitized patients. Therefore, quantitative data on food-specific IgE will not be useful for deciding which sera should be included in a serum bank.

5. Oral challenge test

Case history, SPT and *in vitro* IgE tests, are often not sufficient to discriminate between allergic and sensitized subjects. In many children with atopic dermatitis, <50% of reported food allergies could be substantiated by DBPCFC (Sampson and Ho, 1997). These findings underscore the need to substantiate case histories of food allergy with a DBPCFC. The DBPCFC is the only allergy test that controls for co-morbidity with other chronic disorders (*i.e.*, chronic urticaria, atopic dermatitis), psychogenic factors and observer bias. Furthermore, the DBPCFC is consistently the most accurate method for diagnosing food allergy in older children and adults. An unblinded, food challenge administered by trained personnel is sufficient in infants and young children (Bindslev-Jensen et al., 2004). Although there is no standard procedure for conducting food challenges, some guidelines have recently been published (Bindslev-Jensen et al., 2004).

The preparation of the food used for a food challenge requires knowledge and experience, especially if the allergen is subject to degradation (*i.e.*, fruit and vegetable allergens). Fresh food is recommended and the placebo challenge should match the non-placebo challenge with regard to taste, looks, viscosity, texture, structure and volume. Appropriate sensory testing is important (Vlieg-Boerstra et al., 2004).

A recent study assessed the risk of food challenges in children (Perry et al., 2004). This study documented 253 positive food challenges to egg, milk, peanut, wheat and soy allergens. Twenty-eight percent of the reactions were severe and involved lower respiratory symptoms, but none were severe enough to require hospitalization. No cardiovascular symptoms or late-phase reactions after discharge from the clinic were observed. Severe reactions were less prevalent in patients exposed to a large dose

of allergen than in patients given a lower dose of allergen. Furthermore, the type of food did not correlate with the severity of the reaction (Perry et al., 2004).

It is recommended that the risk and benefit of a food challenge be considered carefully. Food challenge is not recommended in a patient with a history of anaphylactic reaction to food. In these patients, the diagnosis of food allergy should be confirmed without conducting a food challenge.

6. Special considerations

Because children <3 years of age often “outgrow” an allergy to egg, milk and wheat proteins ([Bock and Atkins., 1990], [Bock, 1982], [Saarinen et al., 2005] and [Boyano-Martinez et al., 2002]), testing of blood samples from young allergic children for more than six months after a positive food challenge is not advised. Food allergy is more likely to persist in children who develop food sensitivity after three years of age (Burks and Ballmer-Weber, 2006). For these children, serum sampling should be restricted to 1 (eventually two years) after a positive food challenge. In adult patients, food allergies are often stable. Unfortunately, studies in which food challenges were repeated in allergic adults to assess the course of food allergy are lacking. In general, blood tests for allergies should not be performed for more than three years after a positive food challenge. However, it should be noted that these recommendations are not evidence-based.

7. Conclusions

The minimal criteria for a patient’s serum to be included in a serum bank are: (1) The patient’s case history should provide evidence of immediate-type food allergy accompanied by classical symptoms of type I allergy; and (2) a positive SPT or evidence of elevated food-specific IgE in the serum. Even if these criteria are met, some sera included in the serum bank may be from sensitized patients who do not demonstrate clinical food allergy. In addition, sera from some patients with clinical food allergy will be excluded from the serum bank. A positive DBPCFC is the most reliable criterium for including a serum in a serum bank.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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